however, that the lymphatic drainage of the oesophagus is not segmental, and regardless of the level of the primary tumour metastatic deposits may be found in lymph nodes anywhere between the external jugular vein and the coeliac axis.[9] The frequency of this extensive spread has been shown in recent reports from Japan. At operation the extent of spread to the lymph nodes has been assessed in relation to the level of the primary tumour within the thorax. In one series of 354 patients,[10] almost one-third of those with tumours in the upper or middle third of the oesophagus had spread to the nodes of the upper stomach, while two-thirds of patients with tumours in the lower third had spread to those nodes, 21% had spread to the coeliac nodes, 15% to the splenic nodes, and 10% to the common hepatic artery nodes. Even more disturbing is a report on 36 patients in whom extensive nodal currettings were carried out at operation.[11] Ten of the 36 had "jumping" metastases to nodes in the neck or abdomen with no intrathoracic metastases. Regardless of the level of the primary tumour left supraclavicular nodes were affected in seven patients and, surprisingly, right supraclavicular nodes were affected in nine.

A surgeon contemplating resection for oesophageal carcinoma must therefore decide whether he can indemnify the patient against recurrence at the anastomosis and also against recrudescence elsewhere. Recurrent malignant dysphagia may be prevented by resecting at least 12 cm on either side of visible tumour—even though this may demand resecting most or all of the stomach and most or all of the thoracic oesophagus for tumours at or near the gastric cardia.[12] Continuity should be restored by leading the jejunal or colonic conduit as far as possible from the oesophageal bed—which may still harbour microscopic residual tumour that might later invade and obstruct the conduit. Wide bypass without resection is infinitely preferable to inadequate resection, and the operative mortality is much lower.

The patient cannot be indemnified against recurrent tumour at sites other than the anastomosis. Even if the supraclavicular, mediastinal, coeliac, splenic, hepatic, and gastric lymph nodes were routinely dissected bloodborne metastases may already be present. Roberts recently recommended that mediastinal and abdominal node biopsy should be performed before submitting patients to radical resection.[13] In view of the reported high incidence of spread to the supraclavicular nodes biopsy should be considered before even opening the abdomen or chest—since they are not routinely irradiated in radiotherapy for squamous carcinoma of the oesophagus. If these nodes are affected resection is valueless.

R M KIRK

Consultant Surgeon,
Royal Free Hospital,
London NW3 2QG

[1] Earlam R, Cunha-Melo JR. Oesophageal squamous cell carcinoma. I. A critical review of surgery. *Br J Surg* 1980;**67**:381-90.
[2] Morson B. The spread of carcinoma of the oesophagus. In: Smithers DW, Tanner NC, eds. *Tumours of the oesophagus*. Edinburgh: E & S Livingstone, 1961:136-45.
[3] Pack GT, McNeer G. Surgical treatment of cancers of the gastric cardia. *Surgery* 1948;**23**:976-1019.
[4] Keighley MRB, Moore J, Lee JR, Malins D, Thompson H. Peroperative frozen section and cytology to assess proximal invasion in gastro-oesophageal carcinoma. *Br J Surg* 1981;**68**:73-4.
[5] Miller C. Carcinoma of thoracic oesophagus and cardia. A review of 405 cases. *Br J Surg* 1962;**49**:507-22.
[6] Appelquist P. Carcinoma of the oesophagus and gastric cardia. A retrospective study based on statistical and clinical material from Finland. *Acta Chir Scand* 1972;suppl 430:1-92.
[7] Postlethwait RW, Sealy WC. *Surgery of the esophagus*. Springfield, Illinois: Thomas, 1961.
[8] Logan A. The surgical treatment of carcinoma of the esophagus and cardia. *J Thorac Cardiovasc Surg* 1963;**46**:150-61.
[9] McCort JJ. Radiographic identification of lymph node metastases from carcinoma of the esophagus. *Radiology* 1952;**59**:694-711.
[10] Akiyama H, Tsurumaru M, Kawamura T, Ono Y. Principles of surgical treatment of carcinoma of the esophagus. Analysis of lymph node involvement. *Ann Surg* 1981;**194**:438-46.
[11] Sannohe Y, Hiratsuka R, Doki K. Lymph node metastases in cancer of the thoracic esophagus. *Am J Surg* 1981;**141**:216-8.
[12] Kirk RM. A trial of total gastrectomy, combined with total thoracic oesophagectomy without formal thoracotomy, for carcinoma at or near the cardia of the stomach. *Br J Surg* 1981;**68**:577-9.
[13] Roberts JG. Cancer of the oesophagus—how should tumour biology affect treatment? *Br J Surg* 1980;**67**:791-7.

Ampicillin and alternatives

Since its introduction in 1961 ampicillin has become the antibiotic of choice for the treatment of many infections, as the recommendations in the *British National Formulary* indicate.[1] It is widely prescribed and in a recent survey in a district general hospital 41% of all antibiotic prescriptions were for ampicillin.[2]

Various esters of ampicillin (pivampicillin, bacampicillin, and talampicillin) and related compounds or ampicillin analogues (ciclacillin, epicillin, and amoxycillin) have been developed, but do these other agents have any real advantages over ampicillin? These three esters are hydrolysed to ampicillin after absorption from the gut so that antibacterial activity is identical with that of ampicillin. Epicillin (not available in Britain) is an antibacterial agent in its own right, but its spectrum and activity are similar to those of ampicillin.[3] At best the in vitro activity of ciclacillin is only one quarter that of ampicillin and it performs badly against some Gram negative species.[4] It is more resistant to the effects of staphylococcal β-lactamase than ampicillin but a study in volunteers suggested that there was little difference between the activities of the two drugs in vivo.[5] Amoxycillin also has a spectrum of activity similar to that of ampicillin, but reports of its use in Gram negative infections in mice suggest that it may be more effective in vivo.[6-8] Ampicillin and amoxycillin were given in doses to achieve equal serum concentrations. Although the minimum inhibitory concentrations of the two agents were the same, amoxycillin had a greater protective effect as judged by reduction in size of the infective lesion, number of viable organisms obtained from the lesion,[7] and survival of the animals.[6] In contrast with this work recent studies[9,10] suggest that some Enterobacteriaceae are susceptible to ampicillin but resistant to amoxycillin.

Despite the similarity in their activity the antibacterial agents vary in their pharmacokinetics. Ampicillin is only moderately well absorbed from the gut (about 40% is recovered in the urine). The esters and related compounds are more completely absorbed. Equal oral doses of amoxycillin and ampicillin achieve serum concentrations at a ratio of 2:1,[11,12] and the urinary concentration of amoxycillin is higher. Bacampicillin and talampicillin have similar absorption characteristics to amoxycillin.[13,14] Verbist[15] reported that pivampicillin was better absorbed than amoxycillin, while other authors consider that its absorption is between that of amoxycillin and ampicillin.[16] Peak serum concentrations of ciclacillin are thought to be five times higher than those of ampicillin after equal doses, but the excretion of ciclacillin is fast and the concentrations fall rapidly.[17] The enhanced absorption of amoxycillin, talampicillin, bacampicillin, and pivampicillin means that they may be given less often than

ampicillin; it is suggested that the first two should be given three times a day, and for the last, twice daily. In our opinion, however, doses should be given at least three times a day in treating anything other than trivial infections. In assessing the therapeutic advantage of high serum concentrations Davies and Maesen measured the concentrations of ampicillin in serum and sputum after oral doses of 1 g.[18] The mean serum concentration was 7·8 mg/l, the mean sputum concentration 0·25 mg/l, but 65% of bacterial strains needed 0·25 mg or more ampicillin per litre to inhibit their growth.

They concluded that even doses of 1 g of ampicillin might be insufficient to treat most chest infections due to *Haemophilus influenzae* (although clinical experience may refute this). Agents which achieve higher serum and therefore higher sputum concentrations might have an advantage over ampicillin in such cases.

These agents are not free of side effects. Diarrhoea and rash are said to occur in 8-30%[19 20] and 3-7%,[5 20] respectively, of patients taking ampicillin. The related drugs are claimed to cause fewer side effects because they are better absorbed and, in the cases of bacampicillin, talampicillin, and pivampicillin, the unabsorbed compound remaining in the gut is bacteriologically inactive, so that the intestinal flora is not disturbed. Diarrhoea has been reported in only 2% of patients after amoxycillin[21] and in 5% after ciclacillin.[5] The incidence of rash is said to be reduced to 2% in patients treated with these agents. These compounds, which are converted to ampicillin after absorption, are likely to produce a skin eruption as often as the parent drug. There is, however, a paucity of prospective studies on the incidence of side effects with these agents. True hypersensitivity will occur with equal frequency in all.

Ampicillin has advantage in terms of cost: it is available from five manufacturers and, with the exception of one preparation, it is cheaper than the cheapest ampicillin analogue. A course of amoxycillin 500 mg three times a day is over six times more expensive than the cheapest available preparation of ampicillin 500 mg four times a day. When equivalent serum concentrations are compared, however, amoxycillin 250 mg three times a day does not come out so unfavourably in terms of cost. The prices of the other agents are similar to amoxycillin: bacampicillin, pivampicillin, and talampicillin are cheaper; ciclacillin more expensive.

Should high dose amoxycillin be used to treat urinary and chest infections, thereby simplifying treatment regimens and reducing cost? Several studies of amoxycillin, taken as a single double dose of 3 g, have shown that it is as effective as conventional treatment,[22 23 25] but the conclusion needs to be substantiated by controlled comparative trials with ampicillin. Possibly a high dose regimen may give rise to an unacceptable incidence of side effects. Leigh and colleagues[24] compared a single dose of 3 g amoxycillin with 250 mg three times daily for 10 days. The single dose had a lower cure rate than the full course and a higher incidence of side effects—17·5% of patients had diarrhoea after the 3 g dose as against 3% after the full course. The use of high dose amoxycillin in the treatment of chest infections remains contentious, with some evidence that, in highly selected patients, high dose amoxycillin may be of value.[25] There is less controversy over the use of high dose amoxycillin in preventing endocarditis after dental procedures: 3 g of amoxycillin before surgery and 3 g six to eight hours later would seem appropriate (provided that this does not entail anaesthesia and no penicillins have been used in the previous month).[26]

There is little to suggest that ampicillin should be abandoned in favour of its newer relatives. Certainly almost all the alternatives are better absorbed than the parent compound, but diarrhoea is still fairly common with them all. Increased absorption means that satisfactory serum concentrations may be obtained on a thrice daily regimen, which patients may find more acceptable. The 12 hourly regimen suggested for pivampicillin seems optimistic. In terms of activity the only agent which has some advantage over ampicillin is amoxycillin.

It might be argued that one of the esters should replace ampicillin, but such an argument is unlikely to be sustained in these cost conscious days. The benefits are small and even though serum concentrations after oral ampicillin are lower than those of its rivals, its effectiveness is proved by 20 years of clinical experience. Ampicillin should continue to be widely prescribed within hospitals and outside, even though its relatives may have the edge on it. Certainly no doctor need keep more than one of the group in his formulary, and if cost is no consideration amoxycillin is probably the one to choose.

A DYAS
Senior registrar

R WISE
Consultant

Department of Medical Microbiology,
Dudley Road Hospital,
Birmingham B18 7QH

1 British Medical Association and The Pharmaceutical Society of Great Britain. *British national formulary No 3*. London: British Medical Association and The Pharmaceutical Society of Great Britain, 1982.
2 Moss F, McSwiggan DA, McNicol MW, Miller DL. Survey of antibiotic prescribing in a district general hospital. I: Pattern of use. *Lancet* 1981;ii:349-52.
3 Basch H, Ericksen R, Gadebusch H. Epicillin: in vitro laboratory studies. *Infect Immun* 1971;**4**:44-9.
4 Rosenman SB, Weber LS, Owen G, Warren GH. Antimicrobial activity and pharmacological distribution of Wy-4508, an aminoalicyclic penicillin. *Antimicrob Agents Chemother* 1967:590-6.
5 Gold JA, Hegarty CP, Deitch MW, Walker BR. Double-blind clinical trials of oral cyclacillin and ampicillin. *Antimicrob Agents Chemother* 1979;**15**:55-8.
6 Acred P, Hunter PA, Mizen L, Rolinson GN. α-Amino-p-hydroxybenzylpenicillin (BRL 2333), a new broad-spectrum semisynthetic penicillin; in vivo evaluation. *Antimicrob Agents Chemother* 1970:416-22.
7 Hunter PA, Rolinson GN, Witting DA. Comparative activity of amoxycillin and ampicillin in an experimental bacterial infection in mice. *Antimicrob Agents Chemother* 1973;**4**:285-93.
8 Burns MW, Devitt L. Infections of the lower respiratory tract: treatment with amoxicillin. *J Infect Dis* 1974;**129**, suppl:S194-7.
9 Brumfitt MW, Hamilton-Miller JMT, Dixson S, Gargan RA, Gooding A. Enterobacter resistant to amoxycillin/clavulanate. *Lancet* 1982;ii:768-9.
10 Mittermayer HW. Enterobacter resistant to amoxycillin/clavulanate. *Lancet* 1982;ii:769.
11 Gordon RC, Regamey C, Kirby WMM. Comparative clinical pharmacology of amoxicillin and ampicillin administered orally. *Antimicrob Agents Chemother* 1972;**1**:504-7.
12 Sutherland R, Croydon EAP, Rolinson GN. Amoxycillin, a new semisynthetic penicillin. *Br Med J* 1972;iii:13-6.
13 Bodin NO, Ekström B, Forsgren N, *et al.* Bacampicillin, a new orally well-absorbed derivative of ampicillin. *Antimicrob Agents Chemother* 1975;**8**:518-25.
14 Leigh DA, Reeves DS, Simmons K, Thomas AL, Wilkinson PJ. Talampicillin: a new derivative of ampicillin. *Br Med J* 1976;i:1378-80.
15 Verbist L. Triple crossover study on absorption and excretion of ampicillin, pivampicillin and amoxycillin. *Antimicrob Agents Chemother* 1974;**6**:588-93.
16 Lode H, Janisch P, Küpper G, Weuta H. Comparative clinical pharmacology of three ampicillins and amoxicillin administered orally. *J Infect Dis* 1974;**129**, suppl:S156-68.
17 Hertz CG. Serum and urinary concentrations of cyclacillin in humans. *Antimicrob Agents Chemother* 1973;**4**:361-5.
18 Davies B, Maesen F. Serum and sputum antibiotic levels after ampicillin, amoxycillin and bacampicillin—chronic bronchitis patients. *Infection* 1979;**7**, suppl 5:S465-8.
19 Brogden RN, Speight TM, Avery GS. Amoxycillin: a new review of its antibacterial and pharmacokinetic properties and therapeutic use. *Drugs* 1975;**9**:88-140.
20 Bass JW, Crowley DM, Steele RW, Young FSH, Harden LB. Adverse effects of orally administered ampicillin. *J Pediatr* 1973;**83**:106-8.

[21] Wise PJ, Neu HC. Experience with amoxicillin: an overall summary of clinical trials in the United States. *J Infect Dis* 1974;**129**, suppl:S266-71.
[22] Fang LST, Tolkoff-Rubin NE, Rubin RH. Efficacy of single-dose and conventional amoxicillin therapy in urinary-tract infection localized by the antibody-coated bacteria technic. *N Engl J Med* 1978;**298**:413-6.
[23] Harbord RB, Grüneberg RN. Treatment of urinary tract infection with a single dose of amoxycillin, co-trimoxazole, or trimethoprim. *Br Med J* 1981;**283**:1301-2.
[24] Leigh DA, Marriner J, Fabb S. Treatment of domiciliary urinary tract infections with a single dose of amoxycillin. *J Antimicrob Chemother* 1980;**6**:403-5.
[25] Cole PJ, Roberts DE, Davies SF, Knight RK. A simple oral antimicrobial regimen effective in severe chronic bronchial suppuration associated with culturable Haemophilus influenzae. *J Antimicrob Chemother* (in press).
[26] Shanson DC, Ashford RFU, Singh J. High-dose oral amoxycillin for preventing endocarditis. *Br Med J* 1980;**280**:446.

Writer's cramp

Doctors' attitudes to patients suffering from the so-called occupational neuroses are exemplified by the immortal line of the doctor in *Take it From Here*: "There's a lot of it about but I don't know what it is!" Accordingly, we can only commend an attempt to clarify the clinical nosology of this group of functional disorders, which range from writer's cramp to the "yips" in golfers of the calibre of Sam Snead and Ben Hogan.[1] A recently reported study of 29 such patients with detailed psychological evaluation in each case may not, however, have shed any further light on the nature and pathogenesis of writer's cramp in particular. Sheehy and Marsden[2] have described the clinical characteristics and personality profiles of these patients dividing them into two groups, simple writer's cramp and dystonic writer's cramp (painful muscle spasms affecting manual tasks other than writing) on the basis of Gowers's original classification.[3] They emphasise the low incidence of psychiatric morbidity in their patients in comparison with a control population as assessed by the present state examination and index of definition scores (developed by the Medical Research Council Social Psychiatry Unit at the Institute of Psychiatry). They also found that almost half of the patients with "simple" writer's cramp subsequently developed the dystonic form. On the basis of their data and an extensive re-examination of early published work they concluded that writer's cramp (and related occupational cramps) was a physical illness rather than a psychiatric disorder and that it represented a focal form of dystonia.

In patients with writer's cramp the posture of the affected hand is similar or even identical with that seen in torsion dystonia.[4] Nevertheless, the painful muscle spasms characteristic of writer's cramp and related disorders are induced only by the movements with which they are associated, whereas dystonic posturing in torsion dystonia often develops spontaneously and is not necessarily painful. In writer's cramp spread of the painful spasms to other muscle groups is well recognised, bilateral symptoms developing not uncommonly in people who teach themselves to write with the previously unaffected hand. Several authorities have noted an association between writer's cramp and spasmodic torticollis or other forms of segmental dystonia,[5-9] but there is no published evidence that writer's cramp ever evolves into generalised torsion dystonia—despite the remarkably similar abnormal posture of the hand in the two conditions, as mentioned already. Furthermore, clinical similarities do not imply identity in nosological terms or even a common pathogenesis. Torsion dystonia is an inherited disorder determined by an autosomal dominant trait in most cases, albeit with considerable variability of expression in the affected individual.[4] Patients with writer's cramp occasionally give a family history suggesting that close relatives may have been affected, and Gowers lists a bewildering variety of what were almost certainly chance associations with other neurological disorders prevalent at the time and since (epilepsy, migraine, tabes dorsalis, and general paresis of the insane).[3] Nevertheless, there is no clear cut evidence implicating genetic factor(s) in the aetiology of writer's cramp.

If, then, the similarities between writer's cramp and the dystonias are seen as clinical coincidence, both the aetiology and pathology of the occupational neuroses remain obscure. The second edition of Gowers's classical treatise makes it clear that he had modified his views on the nature of these disorders since the publication of the first edition six years earlier. In particular he dropped the distinction between simple and dystonic forms and in his consideration of its associations and predisposing factors made the point that "no influence is met with so frequently as to deserve special mention, *except anxiety*" (my italics). Further he clearly was no longer assuming the existence of a "writing centre," possibly in the cerebral cortex, as had been the case in his earlier writings.[3] Accordingly he would appear to be a less than entirely reliable pillar on which to base the speculative hypothesis formulated by Sheehy and Marsden. The recent suggestion that neuronal regression in the singing centres in the male canary brain may offer a model for the loss of skills such as writing seems even more improbable.[9a]

To turn to treatment, writer's and other occupational cramps induce in the clinician what can only be described as unrelieved gloom. Some patients are improved in the short term by treatment with benzodiazepines or anticholinergic preparations, and temporary success has been claimed for conditioning therapy,[10] biofeedback,[11] and psychoanalysis,[12] the latter in a patient whose painful cramps were believed to constitute a compensatory mechanism for inadequate penile erection. No long term improvement, however, has ever been achieved by these techniques. In view of this, the last resort is likely to be that advocated by an eminent senior colleague recently asked for advice on the treatment of a Department of Health and Social Security clerk with writer's cramp in the right hand. His reply "Tell him to use the other hand" may be regarded as therapeutic nihilism of the worst kind, although Gowers records a gratifying response to the same approach.[9] His patient, a Government clerk afflicted with writer's cramp on the right, successfully switched to writing with his left hand, continued to work for 12 years, and retired on a pension. *Plus ça change.*

P HUDGSON

Consultant and Senior Lecturer in Neurology,
Regional Neurological Centre,
Newcastle General Hospital,
Newcastle upon Tyne NE4 6BE

[1] Foster JB. Putting on the agony. . . . *World Medicine* 1977;**12**, 19:26-7.
[2] Sheehy MP, Marsden CD. Writers' cramp—a focal dystonia. *Brain* 1982;**105**:461-80.
[3] Gowers WR. *A manual of diseases of the nervous system.* Vol II. 1st ed. London: J and A Churchill, 1886-8.
[4] Zeman W, Dyken P. Dystonia musculorum deformans. In: Vinken PJ, Bruyn GW, eds. *Handbook of clinical neurology.* Vol 6. Amsterdam: North Holland, 1968:517-43.
[5] Babinski J. Spasme facial post-encéphalitique. *Rev Neurol (Paris)* 1921; **28**:462-8.
[6] Barre J-A. La crampe des écrivains, maladie organique, ses formes, ses causes. *Rev Neurol (Paris)* 1952;**86**:703.
[7] Meares R. An association of spasmodic torticollis and writer's cramp. *Br J Psychiatry* 1971;**119**:441-2.